REMARKS

Please amend the title of this application to read "DNA AND RNA CONFORMATIONAL SWITCHES AS SENSITIVE ELECTRONIC SENSORS OF ANALYTES". It is submitted that this title appears in the US national phase entry documents as well as the Request form of the predecessor Patent Cooperation Treaty (PCT) application as originally submitted. It is apparent from the patent specification, for example at paragraphs 65-67, that the applicant's switches may comprise RNA as well as DNA. No new matter has been added.

It is submitted that the Information Disclosure Statement (IDS) originally filed complied with the requirements of 37 CFR 1.97, 1.98 and MPEP § 609 and copies of all of the references were provided to the Examiner in compliance with 37 CFR 1.56. However, to avoid further consideration of this issue, a further IDS accompanies this Amendment listing references not yet initialed by the Examiner. The Examiner is respectfully requested to consider all of the listed citations.

In reply to the Examiner's rejection of claims 1-4, 6-13, 15-23, 25-27 and 29-36 under 35 USC. § 112, first paragraph, it is submitted that the above claims comply with the written description requirement. According to MPEP § 2163 there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed (*In re Wertheim*, 541 F. 2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)) and rejection of an original claim for lack of written description should be rare. It is submitted that the Examiner has not met the burden of presenting evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims.

The applicant submits that a written description of the invention commensurate in scope to the claims under examination appears, *inter alia*, in the Summary of the Invention at paragraphs 10-19 of the application. If the Examiner prefers that such description be reiterated elsewhere in the specification, then the specification could be amended accordingly.

It is submitted that the applicant has clearly provided sufficiently detailed, relevant identifying characteristics of the invention such that a person skilled in the art would recognize that the applicant was in possession of the claimed subject matter. For example, the features recited in claim 1 are described, *inter alia*, at paragraphs 10 and 52-55; Figures 1-2 and the Example

commencing at paragraph 91. More particularly, the applicant describes an analyte sensor comprising a first oligonucleotide stem (e.g. a first DNA strand); a second oligonucleotide stem (e.g. a second DNA strand); and a receptor capable of binding analyte (e.g. a high affinity DNA aptamer for detecting the presence of the analyte adensosine). As indicated at paragraph 92 of applicant's specification, NMR studies have confirmed that this aptamer, upon binding two molecules of adenosine, undergoes an adaptive folding forming a tightly hydrogen-bonded and stacked helical structure. Further, applicant's Example at paragraph 109 of the specification clearly demonstrates that the adenosine-induced folded structure of the aptamer receptor was capable of facilitating charge transfer between the first and second oligonucleotide stems, as recited in claim 1. It is therefore submitted that all of the features of claim 1 are clearly described in applicant's specification.

The guidelines set forth in MPEP § 2163 state that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. As indicated above, the applicant has described an actual reduction to practice of both an integrated-ligand sensor as illustrated, *inter alia*, in Figure 1(b), and Example 2.3.1 and a coupled-ligand sensor as illustrated, *inter alia*, in Figure 1(a), 15(a) and Example 2.3.2. It is submitted that a person skilled in the art would recognize from the applicant's specification, for example at paragraph 114, that the functionality of the coupled-ligand sensor does not depend on the conductivity of the aptamer domain and that there is only a requirement for a conformational change in the receptor upon binding of analyte.

The applicant's specification also describes, for example at paragraph 6, that it is well-known in the art that *in vitro* selection methods are capable of generating a wide variety of aptamer sequences capable of specifically binding a large number of different analytes, including molecular species which do not normally interact with DNA or RNA. Further, a person skilled in the art would recognize that such aptamers are capable of undergoing a conformational change upon binding a cognate ligand analyte. Figure 10 of applicant's specification describes a process for *in vitro* selection of sensors specific for a particular target analyte. The Stanton et al. and

Breaker et al. references cited by the Examiner, which are discussed further below, describes other means for constructing molecular switches comprising nucleic acids which undergo a conformational change upon binding of an effector.

The specification also describes that it is well-known in the prior art that naturally occurring and aptamer binding sites may be made exclusively of RNA. At paragraph 67 of the specification, the applicant describes how the invention may be employed to identify RNA-binding analytes such as the small HIV-coded proteins Tat and Rev, which bind specifically to respective RNA sites in HIV genomic RNA. As described by the applicant, the binding of the analytes results in a conformation change, namely an induced-fit folding of the RNA loops.

The applicant's specification clearly describes how the oligonucleotide stems may be formed from DNA, RNA, DNA/RNA composites and other oligonucleotide constructs including nucleic acid analogues and nucleic acid-like molecules capable of base pairing. It is submitted that such different embodiments would be readily apparent to a person skilled in the art, especially having regard to the prior art literature described in the specification at paragraph 81 and incorporated by reference. Further, as stated in the guidelines set forth in MPEP § 2163, information which is well-known in the art need not be described in detail in the specification.

It is submitted that the guidelines set forth in MPEP § 2163 require that the Examiner consider each claim separately. On pages 3-5 of the Office Action the Examiner has stated generally that the claims are drawn to various listed features without identifying what features correspond with what claims. Although the Examiner has not addressed each of the applicant's claims separately, it is submitted the written description requirement has been satisfied in respect of each of the claims in issue, including claims directed to particular species, such as claim 29 which specifically relates to an adenosine analyte.

It follows from the foregoing that it would be readily apparent to a person skilled in the art that the applicant was in possession of the subject matter of the claims, including the claimed genus and species, as of the application filing date. The applicant notes that no objections have been made in the corresponding European application that the claimed subjected matter was not adequately described. Given these submissions and the strong presumption that an adequate

written description of the claimed invention is present when the application is filed, the Examiner is respectfully requested to withdraw the rejection under 35 USC § 112.

In reply to the Examiner's rejection of claims 1-4, 6-13, 15-23, 25-27 and 29-36 under 35 USC § 103(a), the Examiner is respectfully requested to reconsider this rejection in view of the following comments.

The Examiner has asserted that the above claims are unpatentable over Stanton et al. (US 2003/0087239) and Breaker (Current Opinion in Biotech., Vol. 13, pages 31-39, 2002) in view of the combined teachings of Meade et al. (USPN 6,238,870), Berner et al. (USPN 6,144,869), and Gasper et al. (J. Am. Chem. Soc., Vol. 119, pages 12,762-12,771, 1997).

Stanton et al., as understood, relates to a target activated nucleic acid sensor which results in a change in the optical qualities of the sensor rather than a change in the electrical properties and the charge transfer characteristics. The sensor includes an optical signaling unit which changes its optical properties upon allosteric modulation of the sensor.

Breaker, as understood, relates to RNA and DNA molecules engineered solely to function as enzymes. The engineered molecular switches trigger catalytic events when a target molecule becomes bound. The molecules may be arranged in an RNA array. Breaker does not relate to changes in the transfer of electrical charge. Binding of analyte is detected by means of radioactive labelling (e.g. Figure 5).

Meade et al., as understood, relates to nucleic acid mediated electron transfer, wherein the nucleic acid comprises a covalently attached electron transfer moiety. The moiety is preferably a transition metal complex attached to a single stranded nucleic acid. The construct may be used as a new form of gene probe. Meade et al. does not relate to the sensing of a broad spectrum of analytes resulting from a conformational change when the analyte binds to a specific receptor site as described in applicant's specification.

Berner et al. relates to monitoring of physiological analytes. The analytes are extracted transdermally from a biological system, for example to measure blood glucose levels. Berner et

al., as understood, does not comprise an electronic sensor system comprising oligonucleotide stems operatively coupled to a receptor site.

Gasper et al., as understood, relates to a finding that oxidative damage may migrate in double stranded DNA. A series of duplex DNA structures were prepared that incorporate an anthraquinone group. DNA damage at a location distal from the anthraquinone group following irradiation is due to migration of a radical cation through the duplex DNA. This feature, including a reference to the Gasper et al. reference and the fact that not all perturbations to the helix prevent charge transfer, is referred to at paragraph 3 of the applicant's specification. Gasper et al. does not relate to the sensing of analytes.

The Examiner states that Stanton et al. describes a biosensor that "elicits a detectable signal" when it switches from one conformation state to a second conformational state upon binding of an analyte. As mentioned above, Stanton et al. relates to optical signaling and does not disclose a sensor as recited in applicant's claims where a change in charge transfer results upon analyte binding.

The Examiner states that Breaker "elicits a detectable signal" when the sensor switches from one conformational state to another conformational state. As mentioned above, Breaker also does not relate to changes in the transfer of electrical charge upon binding of analyte. Binding of analyte is detected by means of the release of a cleaved, and radioactively labeled, RNA substrate.

The Examiner acknowledges at page 10 of the Office Action that neither Stanton et al. and nor Breaker teach a sensor which switches from a conformational state which impedes charge transfer to a conformational state where charge transfer is permitted. More particularly, it is submitted that neither of these references disclose a sensor as claimed by the applicant having a structure where a receptor is operatively connected to first and second oligonucleotide stems to effect changes in charge transfer upon binding of an analyte to a receptor.

It is submitted that none of the Meade et al., Berner et al. and Gasper et al. references remedy the deficiencies of Stanton et al. and Breaker. As indicated above, Meade et al. relates to a single stranded nucleic acid having a covalently attached electron transfer moiety. Meade et al. does not describe a specific receptor site operatively coupled to first and second oligonucleotide stems

and is not adapted to detect a wide variety of different analytes. Berner et al. also does not describe an analyte sensor coupled to first and second oligonucleotide stems. The electrode design of Berner et al., as shown in Figure 4, is of an entirely different type and scale than the applicant's invention and does not relate whatsoever to nucleotide and nucleic acid conductivity. As indicated above, Gasper et al. is referred to as general background art in applicant's specification and does not relate to the sensing of analytes.

The Examiner has alleged, at pages 11-13 of the Office Action, that it would be obvious to combine the teachings of the above references to arrive at the subject matter of applicant's claims under examination. Although the Examiner has not considered each claim separately, the applicant assumes that the Examiner is citing all of the references in respect of each claim. References cannot be combined in the absence of some teaching, suggestion or motivation. According to MPEP Chapter 2143, to reject a claim based on combining references, there must be (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations.

It is submitted that there is no teaching, suggestion or motivation in either Stanton et al. or Breaker that any advantage would be achieved by detecting binding of analyte electronically, and particularly by means of a receptor operatively connected to first and second oligonucleotide stems. It is therefore submitted that neither Stanton et al. nor Breaker would look to Meade et al., Berner et al. or Gasper et al. for guidance in modifying their sensors. Moreover, it is submitted that even if such references were combined, they would not result in the subject matter of applicant's claims for the reasons set out above. None of the prior art teach or suggest the idea of connecting a receptor site to oligonucleotide stems in such a manner that binding of analyte to the receptor causes a detectable change in charge transfer between the stems due to a change in conformation of the sensor.

The Examiner refers in particular to the use of rhodium in the paragraph bridging pages 11 and 12 of the Office Action, but this charge flow inducer is referred to only in claim 25 and is not recited in applicant's independent claims or other dependent claims.

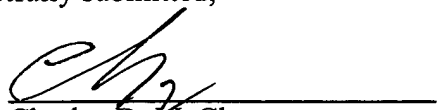
In view of the above submissions, the Examiner is respectfully requested to withdraw the rejection of claims 1-4, 6-13, 15-23, 25-27 and 29-36 under 35 USC § 103(a).

New claims 37-39 correspond to claims indicated as being new and inventive by the European Patent Office in a corresponding European application. It is submitted that such claims relate to the elected species and accordingly should be considered with the claims currently under examination. Claim 37 is similar in scope to currently pending claims 6, 7 and 21 and includes the limitations that the sensor comprises a charge flow inducer and the receptor is an aptamer capable of binding to analytes which do not ordinarily bind to DNA. Claims 38 and 39 are similar in scope to currently pending claims 31 and 32 with the additional features mentioned above now recited in new claim 37.

In reply to the Examiner's provisional obviousness-type double patenting objection at pages 13-14 of the Office Action, the applicant acknowledges that copending Application No. 12/102,669 is a continuation-in-part of the present application and has not yet been examined.

In summary, it is submitted that the Applicant's claims under examination and the newly asserted claims are patentable over the cited references alone or in combination. Accordingly, the Applicant respectfully requests withdrawal of the rejections and allowance of this application. If the Examiner has any questions about this paper, or is not convinced that the claims are in condition for allowance, Applicant requests a personal interview with the Examiner.

Respectfully submitted,

By: 

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on April 16, 2009.

Dated: April 16, 2009

Charles D. McClung